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(54) Esters and amides of indole-, benzo[b]thiophene- or benzo[b]furancarboxylic acids or 4-amino-2-methoxybenzoic acids with N-heterocyclic or N-heterobicyclic alcohols or amines, processes for their preparation, pharmaceutical compositions containing them and applicator for the administration thereof

Compounds with the formula

A—CO—B—D

in which A, B and D possess the meaning indicated in claim 1, processes for their preparation, and pharmaceutical compositions containing them having action against pain, in particular for the treatment of migraine, as antiarrhythmics and for the treatment of gastrointestinal disorders such as gastric secretion disorders, gastritis, peptic ulcer, dyskinesia of the bile tracts, spastic colon, irritable colon, Crohn's disease, ulcerative colitis, carcinoid syndrome and diarrhoea of varying origin (e.g., bacterially induced diarrhoeas, cholangenic diarrhoea, psychogenic diarrhoea) and for the improvement of gastric emptying, for the treatment of gastroduodenal and gastrooesophageal reflux, of oesophageal motility disorders, achalasia, hiatus hernias, cardiac insufficiency, hypotonia of the stomach, pylorus hyperplasia, paralytic ileus and Hirschsprung's disease, and also for the treatment of anxiety states, of psychiatric disorders such as social withdrawal phenomena, manic-depressive psychoses, psychoses and other illnesses connected with stress, disorders of the state of alertness such as geriatric syndromes, and also for the treatment of rhinitis, pulmonary embolism and for the improvement of the nasal absorption of other active compounds, e.g. of peptides, and the inhibition of emesis caused by cytostatics.

Description

The invention relates to compounds with formula I, their preparation, and pharmaceutical compositions containing them according to the claims 1 to 7.

Esters and amides of mono and bicyclic, carboxylic, carbocyclic, and heterocyclic carboxylic acids as well as their antagonistic action on the 5-HT_3 receptor are described in the Belgian patents 8 97 117, 9 00 425, and 9 01 274. The compounds can have because of this property an action against pain as well as antiarrhythmic and antipsychotic actions; in particular, they are active against migraine. In addition, it is specified that the compounds are active in the elimination of serotonin induced gastrointestinal disturbances and in the acceleration of gastric emptying.

According to the invention it was since found that the, within the protection scope of the above mentioned patents contained, but new compounds with formula I according to claim 1, as well as their acid addition salts or quaternary ammonium salts, have an action on the same indications that is superior to that of the in the Belgian patents described compounds. Furthermore, it was found that the compounds are suitable for the treatment of anxiety, psychiatric disorders such as social withdrawal symptoms, manic-depressive psychosis, psychosis and other diseases connected to stress, disorders of the state of alertness such as geriatric syndromes, for the treatment of rhinitis, pulmonary embolism, for the improvement of the nasal absorption of other active compounds, for example, peptides such as salmon calcitonin as well as for the inhibition of an emesis caused by cytostatics.

The groups of formulas III and V can occur in various configurations.

The orientation of the groups III and V can be depicted by means of an equatorial plane that is spanned by the carbon atoms of the piperidyl ring, whereby the nitrogen atom is located above and the alkyl bridge below the plane. The groups III and V have an α-configuration, if the substituent B is located under the plane on the same side as the alkyl bridge. This corresponds to the endo orientation of the tropine, etc. The Substituent B is β-oriented if it is located above the plane on the same side as the nitrogen atom. This is the exo-orientation and the configuration of the pseudotropine, etc. This endo/exo nomenclature is used in the following.

When R_8 stands alkyl in the groups III, V, VI, and VII, then it is in particular methyl.

Group IV is also known as the quinuclidinyl group. Usually, it hereby involves a 3-quinuclidinyl or 4-quinuclidinyl and preferably a 3-quinuclidinyl.

The invention also concerns a process for the production of compounds with formula I as well as their acid addition salt or quaternary ammonium compounds according to the following stage:

Reaction of a corresponding compound with formula VIII,

A—CO—OH (VIII)

in which A has the above meaning or represents a reactive derivative thereof, or a precursor of the acid or of the derivative with a suitable compound with formula IX,

HB—D (IX)

where B and D have the above meaning or represent a precursor of this compound, and preparation of the obtained compounds with formula I as bases or in the form of their acid addition salt or quaternary ammonium salts.

The reaction according to the invention for the production of amides and esters can take place in a manner that is customary for the manufacture of such compounds.

For example, the carboxyl group can be activated through conversion in a reactive acid derivative, in particular for the production of amides. Suitable reactive acid derivatives, such as the carboxylic acid imidazolide or N-hydroxy-succinimide, can be obtained by reaction of the corresponding acids with N, N'-carbonyl diimidazol or n-hydroxy-succinimide. In addition, also acid chlorides can be used, for example, by reaction of the corresponding acids with oxalyl chloride.

Appropriate reaction temperatures are in the range of about -10° to about 10° C. In the case of compounds in which B stands for NH and D for the group IV, the reaction temperature can be up to 100° and the reaction can take place in boiling methanol, ethanol, or dioxane.

Other suitable inert organic solvents are, for example, tetrahydrofuran or dimethoxyethane.

The pure endo- and exo-isomeric reaction products can be separated in a known manner with the aid of chromatography or by crystallization.

The compounds according to the invention can be transformed into other compounds according to the invention, for example, in a known manner.

Insofar as the production of the starting compounds is not specifically described, these are known or can be produced similarly to known compounds, for example, using known procedures for the production of similar compounds.

If desired, also precursors of the starting compounds can be used in the method according to the invention. Such precursors must be capable of being transformed, in a known way, into the starting material. The reaction can also take place using the precursors and other starting compounds or their precursors. The thereby obtained compounds are converted into the compounds of the invention in a known manner, for example, by using the same reaction conditions in which the precursors can be converted into the starting compounds.

The compounds according to the invention can be isolated and cleaned in a known way.

The free bases of the compounds of the invention can be converted into their salts. For example, acid addition salts can be produced in a known manner by reaction with an appropriate acid and vice versa. For the salt formation appropriate acids are hydrochloric acid, malonic acid, hydrogen bromide acid, maleic acid, malic acid, fumaric acid, methanesulfonic acid, oxalic acid, and tartaric acid. Quaternary ammonium salts of the compounds according to the invention can be produced in a known manner, for example, through reaction with methyl iodide. It is self-evident that the acid addition salts and quaternary ammonium acids of compounds with formula I are pharmacologically safe.

In the following examples all temperatures are specified in degrees Celsius and are uncorrected. All NMR spectra are indicated in ppm (tetramethylsilane = 0 ppm).

Example 1

5-Bromo-1H-indole-3-carboxylic acid-endo-8-methyl-u-azabicyclo[3.2.1]oct-3-yl-ester

(Compound with formula I, in which A = II bond in 3-position; R_1 = 5-Br; R_2 = H; X = NH; B = O; D = III in endo-configuration; n = 2; R_8 = CH_3)

6.35 grams (45 mM) endo-8-methyl-8-aza-bicyclo[3.2.1]octane-3-ol (tropine) in 30 ml of absolute tetrahydrofuran is at 0° C to 10° C treated with 17 ml of a 2 molar solution of butyllithium in hexane. The mixture is stirred for 30 minutes and then the hexane is removed in vacuum and is replaced by the corresponding quantity of tetrahydrofuran, whereby the lithium salt is formed.

6.96 grams (27 mM) 5-bromo-indole-3-yl-carboxylic acid chloride in 20 ml of tetrahydrofuran is added to the above mixture and the resulting suspension is stirred overnight at 20° C. The mixture is then reprocessed in the usual way by division between methylene chloride and an aqueous sodium carbonate solution, whereby the in the title mentioned compound is obtained as raw product. This is in silica gel (250 g) chromatographed, whereby methylene chloride, containing 10% methanol and 0.5% ammonia, is used as elution means. The melting point of the in this way obtained racemic compound is 261-262° (methylene chloride/ethyl acetate).

In another embodiment the 5-bromo-indole-3-yl carboxylic acid chloride can be converted with N,N'-carbonyldiimidazol, whereby the imidazolide is obtained. This is with the above lithium salt brought to reaction at 10-15° C in tetrahydrofuran.

Using the method described in the above example 1 and appropriate start compounds, the following compounds with formula I result:

Example	A = II			Bond in position		Group of formula		R_8	Config.	Melt. point (°C)
	R_1	R_2	X	A	B					
2 (+)	H	H	NH	3	O	IV	Bond in 3	-	-	246-247 (Decomp.) (HCL salt)
3	H	2-Me	NH	3	NH	IV	Bond in 3	-	-	283-287 (Decomp.) (HCL salt)
4	H	H	NH	3	O	III	n = 2	C_2H_5	ENDO	298-300 (Decomp.) (HCL salt)
5	H	H	NH	4	NH	IV	Bond in 3	-	-	292-294 (Decomp.)
6	H	H	S	3	NH	IV	Bond in 3	-	-	189-190
7	H	H	NMe	3	NH	IV	Bond in 3	-	-	203-205
8	H	H	NH	3	NH	IV	Bond in 3	-	-	288-290 (Decomp.)
9	H	H	NH	3	O	IV	Bond in 4	-	-	300 (Decomp.)
10	H	2-isoprop.	S	3	O	III	n = 2	CH_3	ENDO	91
11	METHIODIDE OF COMPOUND NR. 10							-	-	285
12 (-)	H	H	NH	3	O	IV	Bond in 3	-	-	245-246 (Decomp.) (HCL salt)
13	H	2-Me	NH	3	O	III	n = 3	H	ENDO	286-287 (Decomp.) (HCL salt)
14	H	2-Cl	NH	3	O	III	n = 2	CH_3	ENDO	239-241 (Decomp.)
15	H	2-Cl	NH	3	O	III	n = 3	H	ENDO	241-242 (Decomp.)
16	5 OH	H	NH	3	O	III	n = 2	CH_3	ENDO	260-262 (Decomp.)
17	H	H	NH	3	O	III	n = 3	CH_3	EXO	210-212 (Decomp.)
18	H	H	S	3	O	III	n = 3	CH_3	ENDO	285-286 (Decomp.) (methiodine)
19	H	H	NH	2	O	III	n = 3	CH_3	ENDO	254 (HCl salt)
20	H	H	NH	7	O	III	n = 3	CH_3	ENDO	152-153
21	H	H	NH	3	NH	III	n = 3	CH_3	EXO	259-261 (Decomp.)

22	H	H	NH	6	O	III	$n = 3$	CH_3	ENDO	132-133
23	H	2-CH_3	S	3	O	III	$n = 2$	CH_3	ENDO	118
24	H	2-CH_3	S	3	O	III	$n = 3$	CH_3	ENDO	94
25	H	H	S	3	O	III	$n = 2$	CH_3	ENDO	274-276 (HCl salt)
26	5-F	H	NH	3	O	III	$n = 2$	CH_3	ENDO	298 (HCl salt)
27	H	H	NH	3	O	VI		CH_3	EXO	179-180 (HCl salt)
28 (+)	5-F	H	NH	3	O	V	Z = OCH_3	CH_3	ENDO	275-276 (HCl salt)
29	H	H	NH	4	O	V	Z = OCH_3	CH_3	ENDO	230-232 (HCl salt)
30	H	H	S	3	O	VII		CH_3	-	171-173 (HCl salt)
31 (+)	H	H	NH	3	O	V	Z = OCH_3	CH_3	ENDO	96-98 (maleinate)
32 (-)	H	H	NH	3	O	V	Z = OCH_3	CH_3	ENDO	88-90 (maleinate)
33	6-OCH_3	H	S	3	O	VII		CH_3	-	45
34	H	H	O	3	O	III	$n = 2$	CH_3	ENDO	276-278 (hydrochloride)

Example	A = IIa		Bond in position			Group of formula	R_8	Config.	Melt. point(°C)
	R_3	R_4	X	A	B				
35	$NHCH_3$	H	-	-	O	III	$n = 3$	H	214-217 (fumarate)
36	$NHCH_3$	J	-	-	O	III	$n = 3$	H	240-241 (fumarate)
37	NH_2	H	-	-	O	III	$n = 3$	H	206-208 (decomp.) (HCl salt)
38	NH_2	J	-	-	O	III	$n = 3$	H	252-253 (decomp.) (HCl salt)

Insofar the compounds are not specified by the sign (+) or (-) as optically active, it involves a racemate.
If there is no specification with respect to a salt it involves the base form.

The compounds according to the invention exhibit a pharmacological action and can therefore be used as pharmaceuticals, for example, for therapy.

In particular, the compounds according to the invention exhibit an antagonistic action on the 5-HT_3 (serotonin) receptor that can be detected with standard tests. For example, in a test, that was described by Riccioppo Neto in the European Journal of Pharmacology (1978) 49, 351-356, it is observed that the compounds of the invention inhibit the influence of serotonin on the level of the action potential of C-fibers on the isolated vagus nerve of rabbits and, namely, under conditions which permit to discriminate between the action potentials that occur in the myelinated nerve fibers (A-fibers) and in the small not myelinated fibers (C-fibers), as was described by B. Oakley and R. Schater in Experimental Neurobiology, A Laboratory Manual, University of Michigan Press, 1978, pages 85 to 96. Serotonin itself acts selectively on the C-fibers and reduces, dose-dependent, the amplitude of the action potential in these fibers. The action of serotonin is not inhibited by the known 5-HT3 antagonists such as Metiteptin [Tr.- this term I could not find anywhere and leave untranslated], methysergide, BOL-148, etc., of which it is assumed that they block the D receptors for serotonin, but not the M receptors (see Gaddam and Picarelli, Brit. J. Pharmacol. (1957), 12, 323-328). It therefore appears that serotonin reduces the level of the action potential of C-fibers under the influence of 5-HT3 receptors that are present on these fibers.

This action can be determined by creating a dose/action curve for serotonin (-10^{-7} -5 x 10^{-6} M). After the action potential of the nerve has stabilized, the serotonin is washed out and, as soon as the C-fiber action potential amplitude has reached the original amplitude, the compound to be investigated is incubated in a concentration of about 10^{-18} M to about 10^{-8} M with the nerve during 30-60 minutes. Different concentrations of serotonin (usually 10^{-7} Mol up to about 10^{-4} Mol) are then used together with the compound according to the invention to be investigated, that is present in concentrations that were present during the duration of the pre-incubation.

The 5-HT_3 receptor antagonists according to the invention block either completely the action of serotonin (non-competitive antagonist), or cause a parallel displacement of the serotonin action curve to the right (that is, higher concentrations of serotonin are needed) (competitive antagonist). The pD'_2 or pA_2 value can be obtained in a known manner.

Another way to determine the 5-HT_3-receptor antagonism is through a test, in which the inhibition of the action of serotonin in concentrations of 10^{-13} to 10^{-6} M on isolated rabbit hearts is measured according to the method of J. R. Fozard and A. T. Mobarok Ali, European Journal of Pharmacology (1978), 49, 109-112. The pD'_2 and pA_2 values can be calculated from it in a known manner.

The actions of the compounds according to the invention as 5-HT_3 antagonists in the treatment of pain is confirmed in the so-called "hot plate test" in, subcutaneous or peroral, doses from 0.1 to 100 mg/kg.

A further investigation to determine the 5-HT_3 antagonism of the compounds can be carried out in humans at concentrations of 10^{-8} M. A blister on the forearm of test subjects is hereby generated by the application of cantharidin. As soon as serotonin comes into contact with the dermis of the blister, pain is generated that can be estimated. The intensity of the pain is proportional to the quantity of administered serotonin. This method is described in detail by C. A. Keele and D. Armstrong in "Substances producing Pain and Itch," Edward Arnold, London, 1964, pages 30-57. This pain generating action of serotonin cannot be inhibited by serotonin-D receptor antagonists, such as lysergic acid diethylamide or its brominated derivatives and it is therefore believed that these are triggered by 5-HT_3 receptors.

According to the described test, hereby the area under the curve is measured and not the peak amplitude of the actions. The area under the curve is recorded by means of a linear integrator that is coupled to a pain indicator and is confirmed by the test person. With increasing concentration of serotonin a cumulative dose/action curve for serotonin is obtained. As soon as, after further supply of serotonin, an action no longer occurs, the serotonin is washed out and the blister is incubated with physiological buffer solution for at least 40 minutes before the administering of the compound according to the invention, for example, the preferred compounds of example 1 or 16. The test compound is pre-incubated with the blister dermis for 30 minutes at concentrations of 10^{-8} M, before different concentrations of serotonin are administered. From this the pA_2 values can be obtained in a known manner.

The compounds according to the invention can be used as 5-HT_3 antagonists, in particular in the treatment of pain, especially migraine, cluster headache, a trigeminal neuralgia, as well as in the treatment of cardiovascular disorders, for example, for the prevention of sudden death as well as antipsychotics.

To achieve the above mentioned therapeutic action, daily doses of 0.4 to 400 mg of the compound according to the invention are advisable, that are effectively administered 2 to 4 times daily in doses of 0.1 to 200 mg or in retard form.

The compounds according to the invention in addition exhibit an anti-arrhythmic action, as can be inferred from their 5-HT_3 antagonistic action in standard tests. For example, the compounds inhibit an arrhythmia that is caused with the aid of norepinephrine in anesthetized rats. In this test norepinephrine infusions of 3 to 10 microgram/kilogram animal body weight are given until an arrhythmic phase that lasts longer than 10 seconds is detected with the aid of EKG measurements. After the control of 3 consecutive administrations of norepinephrine, the compound according to the invention is administered in doses ranging from 10 to about 500 microgram/kilogram animal body weight, followed by an additional norepinephrine administration. The arrhythmic phase is hereby reduced or suppressed depending on the test compound.

The compounds according to the invention are therefore suitable for use as antiarrhythmics. The daily dose to be administered must be in the range of about 0.8 to about 500 mg, which is administered effectively divided into 2 to 4 times daily or in single doses, containing from 0.2 to about 250 mg, or in retard form.

However, the compounds according to the present invention are also suitable for the treatment of gastrointestinal disorders such as gastric secretion disorders, gastritis, peptic ulcer, dyskinesia of the bile tracts, spastic colon, irritable colon, Crohn's disease, ulcerative colitis, carcinoid syndrome as well as diarrhoeas of varying origin (e.g. bacterially induced diarrhoea, cholagenic diarrhoea, psychogenic diarrhoea) and also to improve the stomach emptying, for the treatment of gastroduodenal and gastrooesophageal reflux, esophageal motility disorders, achalasia, hiatus hernias, cardiac insufficiency, hypotonia of the stomach, pylorus hyperplasia, paralytic ileus, and Hirschsprung's disease.

The action of the compounds according to the invention in the treatment of gastrointestinal disorders, in the treatment of gastric secretion disorders, gastritis, ulcer disease, dyskinesia of the bile ducts, spastic colon, irritable colon, Crohn's disease, ulcerative colitis, carcinoid syndrome as well as diarrhoeas of varying origin (e.g., bacterially induced diarrhoea, cholagenic diarrhoea, psychogenic diarrhoea) is demonstrated in pharmacological studies in which the inhibiting action of 5-HT_3 antagonists on the, by serotonin caused, gastrointestinal motility and secretion becomes clear.

In an experimental arrangement the inhibition is measured of the contraction, triggered by serotonin on the isolated longitudinal muscle striae of guinea pigs, by 5-hydroxy-1H-indole-3-yl-carboxylic acid-endo-8-methyl-8-aza-bicyclo[3,2,1]oct-3-yl-ester (compound of example 16, hereafter referred to as compound A), a characteristic representative of the compounds according to the invention.

Extraction of the material

Preparations for the longitudinal muscle striae of the guinea pig with adhering plexus myenteric

Male guinea pigs (200-400 g) are killed by a blow to the head and bled. A part of the small intestine, which is at a distance of about 2 cm from the ileocaecal valve, is taken.

The mesentery is carefully removed and the ileum is put over of a glass rod. The longitudinal muscle layer is cut off with a scalpel and with the aid of a cotton swab dissected by tangential rubbing.

Implementation of the experiment

Longitudinal muscle striae, 3-4 cm long, are put in a bath that contains a Tyrode solution at a temperature of 37°, that is flushed by an oxygen flow that contains 5% carbon dioxide; the Tyrode solution contains the following components (in mMol/l): NaCl 137.0; $CaCl_2$ 1.8; KCl 2.7; $MgCl_2$ 1.05; $NaHCO_3$ 11.9; NaH_2PO_4 0.4; glucose 5.6.

The striae are subjected to a rest-stretching of 500 mg. The contractions are registered with the aid of an isotonic pendular lever. After the adjustment of the balance (over 30 minutes) carbachol - that triggers a reaction - is added in a concentration at intervals of 10 minutes until a corresponding constant action occurs.

Establishment of concentration-reaction curves

Non-cumulative concentration-reaction curves for serotonin are established on the basis of the occurring reactions upon addition of increasing concentrations of serotonin to the organ bath at intervals of at least 15 minutes. For this, one lets the tissue come into contact with each concentration of serotonin for 1 minute. Each stria is only used for recording two concentration-reaction curves; the first one for serotonin alone and the second for serotonin in the presence of a - an inhibition triggering - concentration of the antagonists, i.e., of the compound A. Each stria thus serves as its own control. One lets thereby the antagonists act on the tissue for about 10 minutes before adding the serotonin. The values obtained for the contractions in various preparations are plotted as a percentage of the maximum reaction to serotonin, whereby a logarithmic concentration-reaction curve is obtained. Inhibition constants are expressed in the form of pA_2 values that are determined graphically using standard methods (ARUNLAKSHANA and SCHILD 1959; MacKay 1978).

The contraction caused by serotonin is completely inhibited by adding the compound A in a concentration of 10^{-6} mol/l.

In an additional experimental arrangement the inhibition of the by cholera toxin induced secretion is measured through compound A.

Material and experiment preparation

One lets NMRI mice of the male sex with a weight of 20 to 30 g fast for 24 hours, whereby they have, however, ad libitum water at their disposal. The animals are each pre-treated with 300 µm/kg of compound A by i.p. administration 1 hour before the administration of the cholera toxin.

Execution of the experiment

Each animal is administered 200 µg of cholera toxin with the aid of a probang per os. Thereafter, each is rinsed with 2 ml Tyrode solution (see above). The A compound is

again administered 3 hours after its first administration. The animals are killed 4 hours after the start of the experiment and their intestinal contents is weighed.

0 hours Administration of compound A	1 hours Administration of Cholera toxin	3 hours Second administration of compound A	4 hours Killing of the animals

The intestinal content is in the usual manner increased under the influence of cholera toxin. This process is impeded for about 50% by the administration of compound A in a dose of 300 µg/kg. Increasing the dose of compound A does not lead to a further reduction of the intestinal content.

The compounds according to the invention, for example, compound A, that can be in the form of free bases or in the form of acid addition salts or quaternary ammonium salts, inhibit in the above experiment, at doses above 0.03 to 1.0 mg/kg animal body weight in i.v. administration and in doses from 0.1 to 3.0 mg/kg animal body weight in oral administration, the gastrointestinal motility and secretion caused by serotonin.

The inhibition of the by 5-hydroxytryptophan induced intestine motility increase is measured through compound A in an additional experimental arrangement.

Material and experiment preparation

Male NMRI mice (weight 18-32 g) are withheld food for 20 hours prior to the start of the experiment. Drinking water is not limited. The animals are separated from straw and excrement through a grid. The animals are housed in individual cages at the start of the experiment and they are then also deprived of drinking water.

All animals are pre-treated at the beginning of the experiment with compound A or with a saline solution (control). The application is intraperitoneal, the injection volume is 0.1 ml/10 g. Thirty minutes after the pre-treatment 5-HTP or a saline solution (control) is intraperitoneally administered (injection volume of 0.1 ml/10 g). Immediately afterwards, an activated carbon pulp is perorally administered (10% suspension in water, 0.1 ml/10 g). The animals are killed 45 minutes after the start of the experiment. The large and the small intestine are removed from the stomach to the rectum. For each animal, the transit distance, i.e. the distance that is traveled from the front of the activated carbon pulp in the intestinum. This distance is specified in % relative to the total length stomach-rectum, and is denoted as % transit. Each different treatment method is repeated on at least 3 animals. The individual transit values are averaged.

The strength of the action is specified by ED50. It is the dose, which is capable of reducing by about 50% the motility increase caused by 5-HTP. The ED50 is determined graphically.

The compounds according to the invention inhibit in the above experiment in doses of 0,05-1,0 mg/kg animal body weight in i.v. administration, and in doses of 0.1-3.0 mg/kg animal body weight in oral administration, the gastrointestinal motility increase caused by serotonin that results from 5-hydroxytryptophan.

In addition, it is to be noted that it is an advantage that the non-stimulated, basal motility is not inhibited by the compounds up to very high doses (56 mg/kg).

The compounds of the present invention develop in the acceleration of gastric emptying a very favorable and specific action and are therefore also suitable for the treatment of gastroduodenal and gastrooesophageal reflux, of oesophageal motility disturbances, achalasia, hiatus hernias, cardiac insufficiency, hypotonia of the stomach, pylorus hyperplasia, paralytic ileus, and Hirschsprung's disease.

In the comparison of above mentioned A compound with the known compound METOCLOPRAMID (the MERCK INDEX 1976, Ref 6018) (hereafter referred to as compound B) the action turns out to influence in the "in-vitro" experiment the contraction of the smooth muscles of the stomach and to improve the gastric emptying the "in vivo" experiment.

The "in-vitro" experiment is carried out as described in the following

Male Dunkin-Hartley guinea pigs with a weight of 340 to 450 grams, which have been left without food overnight, are killed by cutting the neck, and the stomachs are removed and placed in a Krebs-Henseleit solution (NaCl 118.0; KCL 4.75; KH_2PO_4 1.2; $MgSO_4$ 1.2; $CaCl_2$ 2.5; $NaHCO_3$ 25.0 and 10 mM glucose). From this segments (approximately 20 mm long, 3-4 mm wide) [Tr.- here only two opening parentheses are present in the original - I assume that the closing parenthesis is intended as in the translation] with a flat cut are cut out that are suitable for the investigation of the voltage changes in the circular muscle layer. The tissue cuts are then put in 30 ml of an organ bath that contains an oxygenic (95% O_2, 5% CO_2) Krebs-Henseleit solution at 37° C.

One gram of tension is applied to the tissue and one lets it then stand for the settling of equilibrium for 45 to 60 minutes before the electrical stimulation is carried out. An intramurale stimulation is achieved with the aid of platinum wire electrodes, which are applied at a distance of about 5 mm, whereby the current is supplied by a Farnell stimulator. Voltage changes are determined with the aid of a Grass voltage transducer and displayed on a multi-channel Grass recording device.

Experimental program

Frequency-reaction curves are first created in the absence of an active substance and then in the presence of a potential effective active substance with a pre-treatment time of 45 minutes. The second curve is related to the first in order to determine the degree of the potentiation or the antagonism. The tissues are stimulated in 5 minute intervals each time for 30 seconds. Fresh tissues are used to determine the interactions with the antagonists. Appropriate solvent control investigations were carried are during all the studies.

Statistical analysis

Reactions are measured as changes in the voltage level; however, the data are modified in such a way that they show the changes as percentages in order to facilitate a comparison between the respective experiments.

"In-vivo" investigations

Measurement of the stomach emptying

The animal is deprived of food 14 hours before the measurement of the gastric emptying. The experiment is carried out with low illumination and little noise and disturbances and only by those experimenters that have daily contact with the guinea pig and have also carried out the initial training in order to make the guinea pigs used to the handling. As a consequence, the animals are subjected only to the smallest amount of stress in this experiment.

The measurement of the gastric emptying is carried out by localization of Kodak plates (NS-2 T, 13 x 18 cm) made of polystyrene-covered barium sulfate spheroids (about 30 with a diameter of 1 mm) with the aid of X-rays (50 KV, 30 mA, 0.5 - 0.8 s). The plates are swallowed by the guinea pigs after they were introduced in the rear part of the snout in 0.2 ml 1% carboxymethyl cellulose with 0.05 ml glycerine to ensure a rapid and voluntary swallowing. The passage of the spheroids is tracked during 3 to 4 hours: the animals are kept in their cages during these periods and are removed only 5 minutes before the investigation by means of X-rays (at 30 to 60-minute intervals) and they are then placed in a holding cage of Plexiglass in which they are kept conveniently in a fixed position: the holding cage is well dimensioned (33 x 15 cm and 13 cm high) to hold a guinea pig with a weight of 450 to 550 g in between foam padded walls and an animal, which was trained to go into the cage, would do this and remain calm and is not stressed during treatment with X-rays.

Experimental program

The gastric emptying is determined as the number of spheroids that leave the stomach. 6 guinea pigs are used in each dose unit of the active substance and the results are compared with those of the guinea pigs that have received the appropriate substrate. The significance of the differences between active substance and control results is established using the Mann-Whitney U test. The average error deviations (S.E.M.s) are calculated from the original data.

Active Substances

The compound A mentioned in the above is as used hydrochloride and compound B as monohydrochloride. The salts are dissolved in distilled water for investigation.

Results

"In-vitro" experiments

An electric field stimulation of a circular muscle that is obtained from the stomach of a guinea pig causes frequency dependent contractions. The contractions are intensified by compound A as well as compound B. The compound A is hereby at least 100 times more active than compound B.

"In vivo" experiments

The i.p. administration of the compounds A and B causes an improvement of the stomach emptying, whereby compound A is in this experiment at least 50 times more active than compound B.

Evaluation of the results

It follows from the results of the above experiment that compound A of the present application has a superior action in the investigations that were carried out. Compound A does not only prove itself to be highly active in the experiments carried out, but they also stand out by virtually lacking side effects.

The compounds according to the invention, that can be in the form of free bases or in the form of acid addition salts or quaternary ammonium salts, improve in the above salt experiments the stomach emptying in guinea pigs in doses from 0.03 to 1.0 mg/kg animal body weight in intravenous administration and in doses of 0.1 to 10.0 mg/kg animal body weight in oral administration.

For the application of the compounds according to the invention for the treatment of gastrointestinal disorders, etc., as well as the improvement of the stomach emptying, etc., the dose of the compounds according to the invention, or their acid addition salts or quaternary ammonium salts, depends on the respective used compound, the administration method, and the desired treatment. In general, however, satisfactory results are obtained with an administration in daily doses of about 0.01 to about 10 mg/kg animal body weight, whereby the administration in smaller doses must take place 2 to 4 times daily or in retard form. For larger mammals the administered daily amount must be about 0.5 to 599 mg, preferably 20 to 100 mg, and in particular 20 to 40 mg. Administration methods, that are suitable for oral administration, must contain 20 to 100 mg of the compounds according to the invention or their acid addition salts or quaternary ammonium salts, together with solid or liquid pharmaceutical substrates or dilution means, and must be administered 2 to 4 times a day.

The compounds according to the invention are generally well tolerated. The compounds also do not show mutagenic actions in the AMES test.

The suitability of the by formula I summarized compounds, and their acid addition salts and quaternary ammonium salts, for the treatment of psychiatric disorders can be inferred from the results of the following experiments:

Study A

A male mouse, held as an intruder in a cage with a domestically held, male, adult mouse, shows little signs of social activity and a strong defensive attitude. Benzodiazepines and similar compounds increase the activity of rapprochement of the intruding mouse in such a situation (DIXON, TRIANGLE 21, 95-105 95-105 [1982], KRSIAK, M., Br. Journal Pharmacol. 55, 141-150 [1975]). The compounds with formula I increase in doses from 0.1 to 1 mg/kg the social activity related to rapprochement.

Study B

Using a slightly modified methodology in comparison to study A with a larger cage, that allows the mouse more freedom of movement, it was found that compound A increases the social behavior of the intruding mouse 45 minutes after i.p. administered doses of 0.01 to 100 micron/kg.

Study C

The situation described in study A is changed, whereby an encounter is included between the male mice which were for 6 hours without food. It turns out that under the formula I summarized compounds, and their acid addition salts and quaternary ammonium salts, prolong in doses from 0.01 to 1 mg/kg the behavior related to rapprochement (K. House Amann, AK Dixon, Physiol. Behav. 1982, 28, 743-745).

Results of studies A, B, and C

In the studies described the under the formula I summarized compounds, and their acid addition salts and quaternary ammonium salts, improve the social relationships of the test animals in such situations, in which stress states would usually impede such behavior. Accordingly, the results of these experiments show that the under the formula I summarized compounds, and their acid addition salts and quaternary ammonium salts, are capable to offset the deterioration of the social behavior caused by stress.

Study D

An extended anticipation posture of the mouse shows an ambivalent conflict situation that is inhibited by the conjecture anxiolytics (Käsermann H. P., Psychopharmacology [1986] 89: 31-37). The compounds with formula I, and their acid addition salts and quaternary ammonium salts, shorten, if they are administered 2 hours in advance, the duration of the extended anticipation posture of mice that are on a raised platform. From this it can be concluded that the compounds are capable to reduce a nonspecific fear, which occurs in stress conditioned circumstances, and thus work anxiolytically.

Study E

Mice placed in a new environment, for example, by moving them from one room to another using a carriage, show an increase in the plasma corticosterone level that can be reduced with benzodiazepine and barbiturates (Lahti R. A., Borsulm C., Res. Comm. Chem. Path. Pharm. 11: 595-603, G. Le Fur et al., J. Pharm. Exp. Ther. 211: 305-308). The compounds with formula I, and their acid addition salts and quaternary ammonium salts, reduce the stress induced corticosterone levels at doses from 0.1 to 10 mg/kg p. o. The compound A reduces the stress induced corticosterone level in doses of 1 to 10 mg/kg p. o., while doses of 0.1 to 0.3 mg/kg increase the plasma levels of this hormone. The profile of the compounds with formula I is in this experiment similar to that of diazepam.

In summary, the results of these studies show that compounds with formula I, and their acid addition salts and quaternary ammonium salts, promote social behavior aimed at engagement in stress induced situations. This suggests that these compounds can be used for the treatment of anxiety and psychiatric disorders in which the treatment of social withdrawal symptoms, manic-depressive psychosis, and other diseases in connection with stress, appears to be appropriate. The increase of the corticosterone level also suggests that these compounds improve the state of alertness and thus offer a possible application in the treatment of disorders of this alertness state, which, for example, occur in geriatric clinical syndromes.

The daily administered doses of the compounds for the indications depend on the nature and severity of the disorders being treated. An appropriate dose range, as suggested by the results of these studies, is about 0.01 to about 50 mg/kg / per person per day, administered in a single dose or in multiple doses.

The compounds with formula I and its salts can be administered for the treatment of psychiatric disorders in the usual way, in particular enterally, preferably orally, for example, in the form of tablets and capsules, or parenterally in the form of injection solutions or suspensions. Suitable pharmaceutical substrates and diluents for oral administration include polyethylene glycol, polyvinylpyrrolidone, mannitol, lactose, etc., granulating means and the disintegration accelerating means such as starch and alginic acid, binders such as stearic acid and gelatin, lubricants such as magnesium stearate, stearic acid, and talc. Suspensions can contain preservatives such as ethyl-p-hydroxybenzoate, suspension means, such as methyl cellulose, surfactants, etc. The parenteral forms are advantageously buffered aqueous solutions (pH between 4 and 5).

For the treatment of rhinitis, pulmonary embolism, and to improve the nasal absorption of other active compounds, for example peptides, it is appropriate to administer via the nasal mucosa the compounds with formula I and their acid addition salts and quaternary ammonium salts.

The nasal track provides a simple and quickly to the target leading administration method which can be easily carried out by the patients themselves, for example, by administering a liquid nasal administration form, for example, a nasal spray or drip solution with the aid of a nasal applicator, or by inserting a with the active compound soaked gelatine-like sponge, as well as by additionally blowing the galenic form as a powder into the nostrils.

In the liquid nasal administration form compounds with formula I, and their acid addition salts and their quaternary ammonium salts, must be present in an amount of 1 to 30%, preferably 5 to 20%, in particular 10 to 15% (weight/volume).

The risk of contamination with pathogenic microorganisms or other undesirable microorganisms must always be considered in particular in the production of liquid nasal administration forms. The procurement of a suitable, fully compatible conservation means to prevent contamination with, for example, pathogenic or other undesirable microorganisms, presents a problem in the production of nasal administration forms. It is particularly critical for nasal pharmaceutical compositions in which the risk of contamination is in particular very high. The preservative must not only be capable to prevent the initial contamination, for example, during the formulation and the filling of the container with the composition, but in addition also the other possible contaminations during use, especially if multiple administrations with a single container/applicator are

required. In particular, problems occur when, for example, a nasal applicator is used again after it has been stored for months - which is often the case. The selected preservative can be inactivated during this phase, for example, by adsorption on the inner walls of the applicator, by heat degradation, or, when the preservative is somewhat volatile, by escaping from the applicator. In addition, there is the danger that, during the actual utilization phase (in multiple administrations with a single applicator this phase can extend over several days or weeks), the applicator will leak or that in another way undesirable microorganisms or other germs penetrate from the atmosphere or from the nostrils into the applicator. Furthermore, the composition can be exposed for shorter periods to higher temperatures, for example, during transport or storage.

In addition to the aforementioned difficulties, a liquid nasal administration form must also be tolerated well, especially at the location of the direct application.

For example, the liquid nasal administration form should neither irritate the nasal mucosa (e.g., cause no significant irritation), nor cause a significant reduction of the frequency of the ciliary movement.

Surprisingly, according to the invention it was found that the for the nasal administration appropriate liquid administration forms containing the compounds with formula I, and their acid addition salts and their quaternary ammonium salts, suffice for the high stability and tolerability standards for a nasal administration and for use in a nasal spray applicators, whereby the administration can take place in multiple doses (blows), i.e., can be preserved in applicators which are capable of delivering a number of individual doses, for example, over a period of several days or weeks, if one uses benzalkonium chloride as a preservative. Surprisingly, it was also found that the use of benzalkonium chloride, even at the lower concentrations that are required for the preservation, favorably influence the nasal absorption of compounds with formula I, and their acid addition salts and their quaternary ammonium salts, and can increase the initial bioavailability of the compounds in the nasal administration.

Accordingly, this part of the present invention concerns in a first aspect a liquid nasal administration form containing

1) compounds with formula I and their acid addition salts and quaternary ammonium salts,
2) a preservative, in particular benzalkonium chloride, and
3) a liquid diluent or a substrate, suitable for administration to the nasal mucosa.

Preferably, the benzalkonium chloride component in the compositions according to the invention is about 0.002 to about 0.02, in particular about 0.01% (weight/volume) of the total composition.

The aforementioned administration forms can according to invention be administered, for example, as drops or as a spray to the nasal mucosa. However, as described below, they are preferably administered as a spray, i.e., as finely distributed droplets. Another possibility to bring the aforementioned liquid nasal administration form into contact with the nasal mucosa, is that one soaks a gelatine-like sponge (SPONGOSTAN) with it and then inserts the sponge into the nostrils.

Advantageously, one uses water (pharmaceutical grade) as a liquid diluent or substrate. Especially preferred is an aqueous salt solution. The liquid nasal administration

forms according to the invention are formulated in such a way that they permit an administration via the nasal track. To this end, they may contain, for example, minimal quantities of additional desired ingredients or excipients, for example, additional preservatives, or, e.g., ciliary stimulants such as caffeine.

The liquid nasal administration forms according to the invention have preferably a pH value of 5.5 to 6.

The liquid nasal administration forms should also have an appropriate isotonicity and viscosity. Preferably, they have an osmotic pressure of approximately 260 to approximately 380 mOsm/liter. The desired viscosity of the compositions according to the invention depends on the administration form in question, e.g., on whether nasal drops or a nasal spray is administered. For nasal drops a viscosity of about 2 to about 40 x 10^{-3} Pa · s is appropriate. For nasal spray a viscosity of less than 2 x 10^{-3} Pa · s is appropriate.

The liquid nasal administration forms can also contain additional components, in particular the usual pharmaceutically applicable surface active agents. In this context, and as another aspect of the present invention, it was found that the use of surface active compounds in the nasal administration of the compounds improves their absorption via the nasal mucosa and the initial bioavailability. In this case, preferred are non-ionic surface active agents, for example, polyoxyalkyl ether of higher alcohols, e.g., with the general formula XXXVI,

$$RO - [(CH_2)_{n'} - O]_x - H \qquad \text{(XXXVI)}$$

in which RO denotes the group of a higher alcohol, in particular a higher alkanol, e.g., lauryl or cetyl alcohol, or an alkylphenol, or sterols, in particular lanosterol, dihydrocholesterol, or cholesterol, as well as mixtures of two of several such ethers. Preferred polyoxyalkyl ethers, that can be used in the present invention, are polyoxyethylene and polyoxypropyl ether (i.e., in which *n'* is in the aforementioned formula 2 or 3), especially lauryl ether, cetyl ether and cholesterylpolyoxy ethylene ether and polyoxypropyl ether, as well as mixtures of two or more such ethers.

Particularly suitable polyethers for use according to the invention are those in which the mean value of repeating units in the polyoxyalkylene part (*x* in the above formula) lies between 4 and 75, in particular between 8 and 30 and, very particularly, between 16 and 26. The polyethers can be obtained according to known methods. A large selection of such products is commercially available and is sold, for example, by the company Amerchol under the brand name Solulan®, by the companies KAO Soap, ICI, and Atlas under the brand name Emalex®, Brij®, and Laureth®, and by the company Croda under the brand name Cetomacrogol®.

Examples of polyoxyalkyl ethers that are suitable for use according to the invention are, for example (POE = polyoxyethylene ether; POP = polyoxypropylene ether; *x* = average of the repeating units in the POE/POP part) are listed below:

1. Cholesteryl ether:
   1.1 Solulan® C-24 - POE, x = 24

2. Ether of lanolin alcohols:

2.1 Solulan® C-16 - POE, x = 16
2.2 Solulan 25 - POE, x = 25
2.3 Solulan® C-75 - POE, x = 75
2.4 Solulan® PB-10 - PPE, x = 10
2.5 Solulan® 98 - POE, x = 10 - partly acetylated
2.6 Solulan® 97 - POE, x = 9 - completely acetylated

3. Lauryl ether:
3.1 Emalex® 709/Laureth ® 9 - POE, x = 9
3.2 Laureth® 4/Brij® 30 - POE, x = 4
3.3 Laureth® 23/Brij® 35 - POE, x = 23

4. Cetyl ether:
4.1 Cetomacrogol® - POE, x = 20 to 24

Lanolin alcohols are also known as wool fat alcohols and they are a mixture of cholesterol, dihydrocholesterol, and lanosterol.

Preferred polyethers for use according to the invention are cholesterylpolyoxyethylene ether, i.e., polyether with formula XXXVI, in which $n' = 2$ and RO is a cholesteryl group, especially those polyethers, in which the number of repeating units of the polyoxyethylene part is 16 to 26, in particular about 24.

Preferably, such polyethers are free of impurities, in particular free of other polyoxyalkylene ethers. They preferably contain at least 75%, in particular preferably at least 85%, and especially preferred at least 90% (weight), of pure cholesterylpolyoxyethylene ethers.

If a surface active agent is used, for example a polyoxyalkylene ether, the quantity of specially used surface active agents that are present in the compounds according to the invention, depends on the administration manner (e.g., as drops or a spray) as well as on the desired action.

In general, the quantity of surface active agents will lie between about 2.0 and about 200 (preferably up to about 100, specifically up to about 20), especially between about 5 and about 30 (preferably up to about 15) and very particularly about 10 mg/ml.

For nasal administration, the liquid nasal administration forms are preferably put in an applicator that is provided with a device that permits the application of the composition to the nasal mucosa, for example, in a nasal spray applicator.

Such applicators are in themselves known and include those that are suitable for the administration of liquid preparations as drops or a spray to the nasal mucosa. Since the dosage of the compounds with formula I, and their acid addition salts and their quaternary ammonium salts, must take place as accurately as possible, the use of spray applicators, with which a precise control of the amount of the administered quantity is possible, is in general preferred. Suitable administration devices are, for example, atomization devices such as pump atomizers or spray cans. In the latter case, the applicator contains a composition according to the invention as well as a propellant that is suitable for use in a nasal spray applicator. The atomization device is provided with an appropriate spraying device which permits the application of the composition to the nasal mucosa. Such devices are generally known.

The container, for example a nasal spray applicator, can contain a quantity of the composition that suffices for a single nasal dose or for the administration of multiple doses, for example, over a period of several days or weeks. The quantity of the single dose corresponds preferably to the aforementioned doses.

The invention concerns accordingly also:

A^V. an applicator containing a liquid nasal administration form which contains the following components:

1) compounds with formula I and their acid addition salts and their quaternary ammonium salts
2) a preservative, in particular benzalkonium chloride, and
3) a liquid diluent or a substrate, that is suitable for the administration to the nasal mucosa,

whereby the applicator is provided with a spraying device that permits the application of the pharmaceutical composition to the nasal mucosa, as well as

B^V. a procedure for the administration of compounds with formula I, and their acid addition salts as well as their quaternary ammonium salts, to people who need such treatment, characterized by that one administers the aforementioned people on the nasal track a galenic form that is suitable for the nasal administration and that contains the in the above under A^V. defined components 1, 2, and 3, as well as, if required, also a surface active agent.

Applicators as defined in the above, are preferably spray applicators for nasal use. They preferably permit the administration of the contained composition in individual doses of about 0.05 to about 0.15 ml, for example, approximately 0.1 ml.

Suitable compositions as well as the individual components 1, 2, and 3 for use in an applicator are those previously described. The doses that can be used for procedure B^V of the invention are also the previously mentioned doses.

In addition, the invention relates to a procedure for producing a liquid nasal administration form containing

1) compounds with formula I and their acid addition salts and their quaternary ammonium salts
2) a preservative, in particular benzalkonium chloride, and
3) a liquid diluent or a substrate that is suitable for the administration to the nasal mucosa as well as, if required, a surface active agent that is suitable for the administration to the nasal mucosa,

whereby the procedure is characterized by that the components are thoroughly mixed together and that the obtained composition is possibly contained in an applicator that is provided with a spraying device that permits the administration of the thus obtained composition to the nasal mucosa. Furthermore, a sponge (SPONGOSTAN) can be soaked in the obtained composition and the thus soaked sponge can be introduced in the nostrils.

The stability of the composition according to the invention can be determined in the usual way.

The compositions according to the invention, containing benzalkonium chloride, are stable against contamination by germs, for example, in accordance with standard tests, as described by S. Urban et al. in Zbl. Bakt. Hyg. I Abt. Orig. B. 1972, 478-484 (1981 and S. Urban, Acta Pharm. Technol. 22, 247-253 (1976). For example, the cell count of standard bacteria, namely E. coli ATCC 8739, Pseud. aeruginosa ATCC 9027, Staph. Aureus ATCC 6538, Strept. pyogenes ATCC 8668, and standard fungi Cand. Albicans ATCC 10231, Sacch. cerevisae ATCC 9763, Aspergillus niger ATCC 16404, and Pen steckii ATCC 10499, is after inoculation of the composition within 24 hours reduced to 0.1% or less, as standard tests show.

The nasal spray composition of the following example 43 was stored in a stability experiment for 3 months in a glass container at 30° C in a nitrogen atmosphere. Pseud. aeruginosa ATCC 9027, Staph. aureus ATCC 6538, Strept. pyogenes ATCC 8668, and the fungi Cand. Albicans ATCC 10231, Sacch. cerevisae ATCC 9763, Aspergilles niger ATCC 16404, and Pen stechii ATCC 10499, were added up to a cell count of approximately 2×10^5 organisms in the inoculated liquid. The number of bacteria has decreased to less than 0.1% within 2 hours. Germs could no longer be detected within 4 weeks.

Furthermore, the compositions are well tolerated as standard tests show, for example, less than 50% inhibition of the ciliary movement frequency is observed 20 minutes after the administration, according to the micro-photo oscillographic method of L. Chevance et al., Acta Otolaryng. 70, 26-28 (1970).

The liquid nasal administration form according to the invention has advantageous properties, in particular, it permits after administration a rapid intake of the active substance in the body. Thus, 200 ng of the aforementioned compound A can be detected in plasma already about 5 to 10 minutes after nasal administration. In oral administration, this active substance concentration in plasma is obtained only after about 30 to 40 minutes. The general bioavailability of the compounds with formula I, and their acid addition salts and their quaternary ammonium salts, has over a period of 6 hours after nasal administration the same order of magnitude as after oral administration.

The same favorable results are obtained if the compounds with formula I and their acid addition salts as well as their quaternary ammonium salts are administered a galenic form that is in the form of a powder, and is introduced by blowing into the nostrils.

A favorable action of the compounds according to the invention against rhinitis is achieved when administered to the nasal track. This is expressed in a reduction of the nasal fluid secretion. It is thereby an advantage that the application of the substances do not deteriorate the ciliary motion of the nasal mucosa.

Required doses: 0.01 mg to 1 mg/dose applied one to several times a day.

The determination of the action of compound A on pulmonary embolism can take place as described as follows:

Reflex investigations were carried out on spontaneously breathing rabbits that were anesthetized with a continuous infusion of sodium pentobarbital. Both vagi remain intact and the systemic arterial blood pressure, the heartbeat, the air breathing volume, the respiratory rate, and the platelet count were recorded.

Control of the embolism reflex

The injection of 1 mg Sephadex G-25 pellets suspended in 0.2 ml Dextran (6%) in 1 minute intervals in 6 control rabbits caused embolism reflexes. The pre-treatment with compound A produced an improvement of the a) mortality and b) the cardiovascular and respiratory reflex -reactions to the miliary pulmonary embolism are analyzed. The results show a clear preventive action of compound A on pulmonary embolism.

The compounds with the formula, and their acid addition salts and quaternary compounds, surprisingly increase the absorption of other active substances, in particular those with a peptidic structure, for example, salmon calcitonin if they are together nasally administered.

For example, in the combined use of compound A (15 mg) and salmon calcitonin (100 IU), of which each half is introduced in each nostril, the bioavailability of salmon calcitonin (AVC up to 2 hours) increases in rhesus monkeys of 0.08 IU/ml/h in the plasma from 1.632 IE/ml/h.

To achieve a favorable action in the above indications, the compounds with formula I, and their acid addition salts quaternary compounds, must be supplied to the body in a dose of 0.01 mg/kg to about 10 mg/kg animal body weight. In humans, the daily dose to be orally administered must be 5 mg to 300 mg of a compound with formula I that is administered in an appropriate manner, for example, in divided doses up to 4 times daily as in the case of compound A with an order of magnitude of about 40 mg/p.o.

For nasal administration, the dose must be 0.13 to 0.4 mg per kilogram of body weight, i.e., about 100 mg to 300 mg or 10 to 30 doses of nasal sprays per patient.

For the joint administration with another active substance the administered amount of a compound according to the invention depends on other active substances and the type of treatment. Usually, one uses half and up to 1/10 the dose of the other active substance.

The compounds with formula I, and their acid addition salts and quaternary compounds, also inhibit vomiting caused by the cancer treatment with cytostatics in animals as standard tests show, for example, by inhibiting the vomiting caused by cisplatin (10 mg/kg i.v.) in ferrets in doses of about 0.005 to about 0.5 mg/kg i.v. (according to the method described in the European patent application 2 01 165).

Accordingly, the compounds of the formula, and their acid addition salts and quaternary compounds, can be used for the treatment of an emesis caused by cytostatics.

The compounds can be included in the following pharmaceutical compositions.

Example 39

Tablets for oral administration

Tablets containing the ingredients cited below are produced in a known manner and used in the described indications.

Compound A in the form of hydrochloride (equivalent to 15 mg of free base)	16.8 mg
hydroxy-propyl-cellulose	1.2 mg
cornstarch	12.0 mg
lactose	93.0 mg
silica gel	0.6 mg

magnesium stearate	1.4 mg
tablet weight	125.0 mg

Example 40

Capsules for oral administration

Capsules that contain the below specified ingredients are produced in a known manner and used in the described indications.

Compound A in the form of hydrochloride (equivalent to 15 mg base)	16.8 mg
Lactose	29.0 mg
Silica gel	1.2 mg
Magnesium stearate	3.0 mg
Capsule content weight	50.0 mg

Example 41

Injection solutions for i. v. administration

An indication solution is produced in a known manner and used in a dose of 10 mg of the active ingredient per day in the described indications.

	A	B	C
Compound A in the form of the hydrochloride	1.12[1])	2.24[2])	11.20[3])
Acetic acid (99 to 100%)*)	1.2	0.6	0.6
Sodium acetate 3 • H_2O*)	1.8	3.18	3.18
Sodium chloride	8.0	7.5	6.5
Water for injection, 1,0 ml			

[1]) = 1 mg free base;

[2]) = 2 mg free base;

[3]) = 10 mg free base; pH value = 4,3;

*) = utilized buffer 1/30 Molar.

Example 42

Capsules for oral administration

5 mg and 15 mg capsules (subsequently A and B), containing the ingredients below, are produced in a known manner and used in the above indication 2 to 4 times daily in the case of the composition A and once daily in the case of the B composition.

	A mg	B mg
Compound A in the form of the hydrochloride	5,60	16.80
Lactose (200-Machine filter)	85.00	79.30
Lactose (100-Machine filter)	84.40	79.30
Cornstarch	120.00	120.00
Silica gel	2.00	1.60
Magnesiumstearat	3.00	3.00
	300 mg	300 mg

Example 43

Nasal composition for the treatment of rhinitis, pulmonary embolism, or to improve the nasal absorption of other active substances

Ingredients	Quantity of the ingredients
5-hydroxyindol-3-yl-carboxylic acid-endo-8-methyl-8-aza-bicyclo[3,2,1]oct-3-yl-ester.HCl	100 mg
Benzalkonium chloride	0.1 mg
NaCl (0.9% aqueous solution)	0.6 ml
Distilled water	0.4 ml

The resulting solution is filtered (e.g., through a 0.2 µm filter) and poured into a nasal spray can or a gelatine-like sponge (SPONGOSTAN) is soaked in it.

Example 44

Nasal composition for the treatment of rhinitis, pulmonary embolism, or to improve the nasal absorption of other active substances

Ingredients	Quantity of the ingredients
5-bromo-1H-indole-3-carboxylic acid-endo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl ester	50 mg
Benzalkonium chloride	0.1 mg
NaCl (0.9% aqueous solution)	0.83 ml
Distilled water	0.17 ml

The resulting solution is filtered (e.g., by a 0.2 µm filters) and poured into a nasal spray can or a gelatine-like sponge (SPONGOSTAN) is soaked in it.

All the in examples 1-38 mentioned active substances can be used for the specified indications in the compositions according to the examples 39-44.

According to the present invention, compounds with formula I are produced, which can be used in a pharmaceutically acceptable form, for example, in the form of free bases or in the form of pharmaceutically acceptable acid addition salts or quaternary ammonium salts for use as pharmaceuticals, in particular because of their use as 5-HT_3 antagonists, for the treatment of such diseases, where the blocking of 5-HT_3 receptors are expected to give rise to a favorable action, for example, as a remedy for pain, in

particular anti-migraine agents, such as antiarrhythmics, as an agent against by serotonin caused gastrointestinal motility and secretion and as an agent for the acceleration of stomach emptying, but also for the treatment of anxiety, psychiatric disorders such as social withdrawal symptoms, manic-depressive psychosis, psychosis and other diseases in connection with stress, disorders of the alertness state such as geriatric disease syndromes, for the treatment of rhinitis, pulmonary embolism, for the improvement of the nasal absorption of other active substances as well as for the inhibition of vomiting caused by the cancer treatment with cytostatics, for example, with cisplatin.

The preferred use is in the field of agents to combat the pain, especially migraine, as antiarrhythmics, for the treatment of gastrointestinal disorders such as gastric secretion disorders, gastritis, peptic ulcer, dyskinesia of the bile ducts, spastic colon, irritable colon, Crohn's disease, ulcerative colitis, and carcinoid syndrome as well as diarrhoeas of varying origin (e.g., bacterially induced diarrhoea, cholangene diarrhoea, psychogenic diarrhoea), as well as for the improvement of stomach emptying, for the treatment of gastroduodenal and gastrooesophageal reflux, oesophageal motility disorders, achalasia, hiatus hernias, cardiac insufficiency, hypotonia of the stomach, pylorus hyperplasia, paralytic ileus, Hirschsprung's disease, and in addition of anxiety, psychiatric disorders, as well as rhinitis, pulmonary embolism, and for the improvement of the nasal absorption of other active substances, e.g., peptides, whereby for the treatment of rhinitis, pulmonary embolism, and the improvement of the nasal absorption of other active substances, the nasal compounds are administered in a for a nasal administration suitable galenic form.

Very especially preferred is the use for the inhibition of an emesis caused by cytostatics, in particular by cis-platinum.

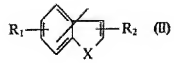
The compounds according to the invention can be administered in the form of free bases or in the form of pharmaceutically acceptable salts, for example, suitable acid addition salts and quaternary ammonium salts. Such salts have the same action with the same order of magnitude as the free bases.

The present invention relates consequently to a pharmaceutical composition that contains a compound with formula I, an acid addition salt thereof, or a quaternary ammonium salt of it, together with a pharmaceutical substrate or diluent. Such compounds can be produced in a known manner and can be administered, for example, in the form of solutions or tablets or the described nasal forms.

1. Compounds with the formula

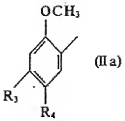
A–CO–B–D (I)

in which A denotes a group with the formula



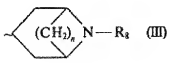
(II)

or the formula



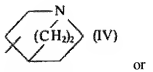
(II a)

in which X, R_1, R_2, R_3, R_4, and B have meanings specified below and D can be selected from the following groups



(III)

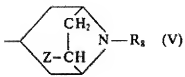
or



(IV)

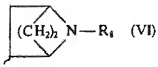
or

(bond in 3 or 4)



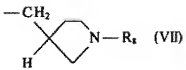
(V)

or



(VI)

or



(VII)

Compound	A = II					Group of formula			
	R_1	R_2	X		B			R_8	Config.
1	5-Br	H	NH	3	O	III	$n = 2$	CH_3	ENDO
2 (+)	H	H	NH	3	O	IV	Bond in 3	-	-
3	H	2-Me	NH	3	NH	IV	Bond in 3	-	-
4	H	H	NH	3	O	III	$n = 2$	C_2H_5	ENDO
5	H	H	NH	4	NH	IV	Bond in 3	-	-
6	H	H	S	3	NH	IV	Bond in 3	-	-
7	H	H	NMe	3	NH	IV	Bond in 3	-	-
8	H	H	NH	3	NH	IV	Bond in 3	-	-
9	H	H	NH	3	O	IV	Bond in 4	-	-
10	H	2-isoprop.	S	3	O	III	$n = 2$	CH_3	ENDO
11	METHIODIDE OF COMPOUND NR. 10							-	-
12 (-)	H	H	NH	3	O	IV	Bond in 3	-	-
13	H	2-Me	NH	3	O	III	$n = 3$	H	ENDO
14	H	2-Cl	NH	3	O	III	$n = 2$	CH_3	ENDO
15	H	2-Cl	NH	3	O	III	$n = 3$	H	ENDO
16	5 OH	H	NH	3	O	III	$n = 2$	CH_3	ENDO
17	H	H	NH	3	O	III	$n = 3$	CH_3	EXO
18	H	H	S	3	O	III	$n = 3$	CH_3	ENDO METHIODIDE
19	H	H	NH	2	O	III	$n = 3$	CH_3	ENDO
20	H	H	NH	7	O	III	$n = 3$	CH_3	ENDO
21	H	H	NH	3	NH	III	$n = 3$	CH_3	EXO
22	H	H	NH	6	O	III	$n = 3$	CH_3	ENDO
23	H	2-CH_3	S	3	O	III	$n = 2$	CH_3	ENDO
24	H	2-CH_3	S	3	O	III	$n = 3$	CH_3	ENDO
25	H	H	S	3	O	III	$n = 2$	CH_3	ENDO
26	5-F	H	NH	3	O	III	$n = 2$	CH_3	ENDO
27	H	H	NH	3	O	VI		CH_3	EXO
28 (+)	5-F	H	NH	3	O	V	Z = OCH_3	CH_3	ENDO
29	H	H	NH	4	O	V	Z = OCH_3	CH_3	ENDO
30	H	H	S	3	O	VII		CH_3	-
31 (+)	H	H	NH	3	O	V	Z = OCH_3	CH_3	ENDO
32 (-)	H	H	NH	3	O	V	Z - OCH_3	CH_3	ENDO
33	6-OCH_3	H	S	3	O	VII		CH_3	-
34	H	H	O	3	O	III	$n = 2$	CH_3	ENDO

Compound	A = IIa					Group of formula	R_8	Config.
	R_3	R_4	X		B			
35	$NHCH_3$	H	-	-	O	III	$n = 3$	H
36	$NHCH_3$	J	-	-	O	III	$n = 3$	H
37	NH_2	H	-	-	O	III	$n = 3$	H
38	NH_2	J	-	-	O	III	$n = 3$	H

as well as their acid addition salts or quaternary ammonium salts.

2. Method for the production of compounds with formula I according to claim 1 as well as their acid addition salts or quaternary ammonium salts, characterized by the reaction of a compound with formula VIII,

A—CO—OH (VIII)

in which A has the above meaning or represents a reactive derivative thereof, or a precursor of the acid or derivative with a suitable compound with formula IX,

HB—D (IX)

where B and D have the above meaning or represent a precursor of this compound, and preparation of the obtained compounds with formula I as bases or in the form of their acid addition salt or quaternary ammonium salts.

3. Therapeutic composition containing compounds according to claim 1.

4. Therapeutic composition according to claim 3 for use against pain, especially for the treatment of migraine, as antiarrhythmic and for the treatment of gastrointestinal disorders such as gastric secretion disorders, gastritis, ulcer disease, dyskinesia of the bile ducts, spastic colon, irritable bowel, Crohn's disease, ulcerative colitis, carcinoid syndrome and diarrhoea of varying origin (e.g., bacterially induced diarrhoea, cholagenic diarrhoea, psychogenic diarrhoea) and for the improvement of stomach emptying, for the treatment of gastroduodenal and gastrooesophageal reflux, oesophageal motility disturbances, achalasia, hiatus hernias, cardiac insufficiency, hypotension of the stomach, pylorus hyperplasia, paralytic ileus, Hirschsprung's disease, furthermore for the treatment of anxiety, psychiatric disorders such as social withdrawal symptoms, manic-depressive psychosis, psychosis and other diseases connected to stress, disorders of the alertness state such as geriatric disease syndromes, and in addition for the treatment of rhinitis, pulmonary embolism, and the treatment of the nasal absorption of other active substances, for example, peptides as well as the inhibition of an emesis caused by cytostatics.

5. A nasal administration form characterized by that these compounds with formula I, and their acid addition salts and quaternary ammonium salts, contain a preservative as well as a liquid diluent or a suitable substrate for the application to the nasal mucosa.

6. A nasal administration form according to claim 5 for use against rhinitis and pulmonary embolism and for the improvement of the nasal absorption of other active substances, for example, peptides.

7. An applicator for administering a dose of an administration form according to claim 5.